

## Original Article

## Pediatric brain death in a Japanese pediatric hospital

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**Aim:** The Organ Transplantation Act was revised in Japan in 2010, which permitted the organs of children younger than 15 years to be donated after brain death. As of August 2012, 2 years after the Act was revised, only two children had become brain dead donors. In our hospital, we used a basic determination of brain death in order to predict the neurological outcome. We evaluated the incidence and characteristics of pediatric brain death treated at our hospital in order to investigate why there are so few pediatric brain deaths in Japan.

**Methods:** We evaluated the characteristics of patients undergoing a basic determination of brain death and the procedure for the determination was compared retrospectively by reviewing their medical records. We enrolled 3,721 patients aged younger than 15 years who were admitted to the pediatric intensive care unit between 2008 and 2012.

**Results:** A basic determination of brain death had been enacted in 35 patients. Many of the patients undergoing the determination were admitted after resuscitation (pre-group / post-group, 50%/74%) and many of them had been transferred from the emergency department (94%/89%). After revision of the Act, only three children were deemed to be brain dead in our hospital, which was 0.1% of total pediatric intensive care unit admissions and 7% of total pediatric intensive care unit deaths.

**Conclusions:** The low incidence of pediatric brain death in Japan may be due to differences in exclusion criteria for determination of brain death and personal views regarding life and death compared with other countries.

**Key words:** Determination of brain death, critically ill children, pediatric intensive care, organ donation, terminal care

## INTRODUCTION

IN 1985, CRITERIA for the determination of brain death in individuals aged 6 years or older were established in Japan. After the Organ Transplantation Law was enforced in 1997, organ donation from brain dead donors was permitted only when individuals had a documented will of their organ donation and their family did not refuse both the determination of brain death and organ donation. In 1999, organ transplantation from brain dead donors was carried out in Japan. However, the guidelines for application of the Law state that the documented will of organ donation will be accepted from individuals aged 15 years or older. As a result, children younger than 15 years of age were still ineligible to become organ donors after brain death, although criteria for the determination of brain death in children aged 6 years or younger were established in 1999.

After the revised Organ Transplantation Act went into effect on July 17, 2010, even if an individual's intention is unclear, it became possible to donate organs under family consent. Children younger than 15 years who cannot legally express the documented will of organ donation can also donate their organs after brain death. As of August 2012, 2 years after revision of the Act, only two children have become brain dead donors. In Japan, the incidence and characteristics of pediatric brain death are unknown and there has been insufficient research to explain why brain death is diagnosed in so few children.

Our hospital, the National Medical Center for Children and Mothers (Tokyo, Japan), is a 490-bed hospital with a 20-bed Pediatric Intensive Care Unit (PICU). There were 30,832 emergency room visits and 1,072 PICU admissions in 2011, which is the greatest number of critically ill children in a single center in Japan. Furthermore, even before revision of the Organ Transplantation Act, we carried out a basic determination of brain death in order to predict the neurological prognosis of patients.

In this study, we evaluated the incidence and characteristics of pediatric brain death treated at our hospital in order to investigate why there are so few pediatric brain deaths in Japan.

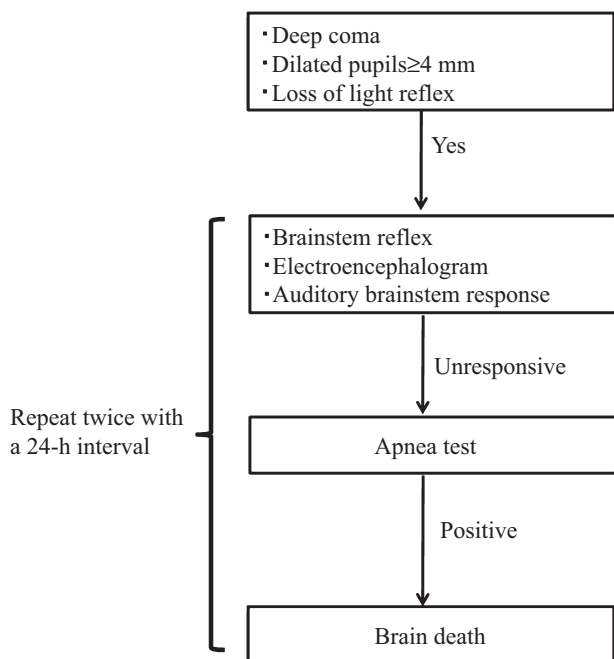
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## METHODS

### Basic determination of brain death at our hospital

THE ORGAN TRANSPLANTATION Act defines three classes for determination of brain death: *legal determination of brain death* performed before an organ donation,



**Fig. 1.** Basic determination of brain death in our hospital is carried out when a patient is in a deep coma and both pupils are dilated to 4 mm or more and fixed. Only when there are absences of brainstem reflexes, brain waves on the electroencephalogram, and auditory brain stem response, an apnea test is carried out, unless the patient's general condition is unstable. When the apnea test is positive, a second determination is carried out a minimum of 24 h later.

*clinical determination of brain death* performed before legal determination of brain death, and *basic determination of brain death* performed to predict a patient's neurological prognosis or to make treatment decisions.

A basic determination of brain death is carried out when a patient is in a deep coma, and both pupils are dilated to 4 mm or more and fixed. We carried out a basic determination of brain death by following the procedures in the Manual for Legal Determination of Brain Death (Fig. 1) (Table 1). Only when there are absences of brainstem reflexes, brain waves on the electroencephalogram, and auditory brain stem response, an apnea test is carried out, unless the patient's general condition is unstable. In the apnea test, apnea is concluded when no breathing effort is observed at the PaCO<sub>2</sub> level over 60 mmHg; this indicates that the apnea test is positive. When the apnea test is positive, a second determination is carried out a minimum of 24 h later. In all cases, we carry out the basic determination of brain death under family consent and notify that result to the family.

We are developing a system to deal with the determination of brain death at our hospital by creating a brain death protocol and performing simulation training, as well as by promoting collaboration between clinical technicians and specialists.

We enrolled patients aged younger than 15 years into the study who were admitted to the PICU at our hospital between July 2008 and June 2012. The patients were divided into two groups depending on the period of PICU admission before or after the revision of the Organ Transplantation Act on July 2010. The cases admitted to our PICU during the 2-year period between July 2008 and June 2010 were categorized as belonging to the pre-group; cases admitted in the 2-year period between July 2010 and June 2012 were categorized as belonging to the post-group. The patients were further divided into two groups for whom a basic determination of brain death was performed (indicated-group) or not (non-indicated-group).

**Table 1.** Criteria for legal determination of brain death in Japan

	12 weeks ≤ age < 6 years	6 years ≤ age < 15 years	≥15 years
Instruction manual	Manual for Legal Determination of Brain Death		
Body temperature	≥35°C	≥32°C	
Systolic blood pressure, mmHg	Age <1 year, ≥65; age 1–13 years, ≥(age × 65); >13 years, ≥90		
Measurement interval	≥24 h	≥6 h	
Determination	Performed by at least two specialists <sup>†</sup>		

†Legal determination of brain death can be performed by specialists authorized by the Japan Neurosurgical Society, Japan Society of Neurology, Japan Association for Acute Medicine, Japan Society of Anesthesiologists, Japanese Society of Intensive Care Medicine, or Japan Pediatric Society.

We retrospectively evaluated the characteristics of patients undergoing a basic termination of death, and the procedure for a basic determination of brain death, by reviewing their medical records. We assessed the number of patients, their age and sex, whether cardiopulmonary resuscitation was carried out before admission, route of admission, and mortality rate. We also evaluated whether the patients included in

the indicated-group met any of the exclusion criteria for legal brain death determination.

Values were expressed as the median value for each group, and statistical processing was carried out using the Mann–Whitney *U*-test, with a *P*-value less than 0.05 considered to indicate a statistically significant difference.

## RESULTS

A TOTAL OF 3,721 patients aged younger than 15 years were admitted to the PICU: 1,712 during the first period of the study and 2,009 during the second period (Table 2). A basic determination of brain death was carried out in 16 patients admitted during the first period and 19 patients admitted during the second period (Table 3).

We compared the variables obtained before and after the revision of the Organ Transplantation Act. Even though there were significant differences in the percentage of resuscitated cases after cardiac arrest and the route of admission in all cases, there were no differences in the patients undergoing a basic determination of brain death.

### Characteristics of patients undergoing basic determination of brain death

Many patients undergoing a basic determination of brain death had been resuscitated after cardiac arrest (pre-group / post-group, 50%/74%) and were transferred from the emergency department (94%/89%) (Table 3).

**Table 2.** Characteristics of all Pediatric Intensive Care Unit (PICU) admissions at the National Medical Center for Children and Mothers (Tokyo, Japan), July 2008–June 2010 (pre-group) and July 2010–June 2012 (post-group)

	Pre-group <i>n</i> = 1,712	Post-group <i>n</i> = 2,009
Age, months <sup>†</sup>	19 (0–179)	24 (0–179)
Sex, male : female	961:751	1,087:922
Resuscitated before PICU admission <sup>‡</sup>	55 (3)*	37 (2)*
Route of admission		
From the operating room <sup>‡</sup>	832 (49)*	1,152 (57)*
From the hospital ward <sup>‡</sup>	375 (22)*	194 (10)*
From emergency room <sup>‡</sup>	505 (29)*	663 (33)*
Mortality <sup>‡</sup>	46 (2.7)	43 (2.1)

†Median (minimum—maximum), ‡Number of cases (% of total no.). \**P* < 0.05.

**Table 3.** Characteristics of patients admitted to the Pediatric Intensive Care Unit (PICU) at the National Medical Center for Children and Mothers (Tokyo, Japan), July 2008–June 2010 (pre-group) and July 2010–June 2012 (post-group)

	Pre-group <i>n</i> = 1,712		Post-group <i>n</i> = 2,009	
	Non-indicated group <i>n</i> = 1,696	Indicated group <i>n</i> = 16	Non-indicated group <i>n</i> = 1,990	Indicated group <i>n</i> = 19
Age, months <sup>†</sup>	18 (0–179)	23 (0–148)	24 (0–179)	35 (0–164)
Sex, male : female	952:744	9:7	1,077:913	10:9
Resuscitated cases before PICU admission <sup>‡</sup>	47 (3)*	8 (50)*	28 (1)**	14 (74)**
Route of admission				
From the operating room <sup>‡</sup>	832 (49)*	0*	1,151 (58)**	1 (5)**
From the hospital ward <sup>‡</sup>	374 (22)	1 (6)	192 (10)	2 (11)
From emergency room <sup>‡</sup>	490 (29)*	15 (94)*	646 (32)**	17 (89)**
Mortality rate <sup>‡</sup>	36 (2)*	10 (63)*	26 (1)*	17 (89)*

Groups were divided according to whether basic determination of brain death was carried out (indicated-group) or not (non-indicated-group).

\**P* < 0.05.

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## Procedure for basic determination of brain death

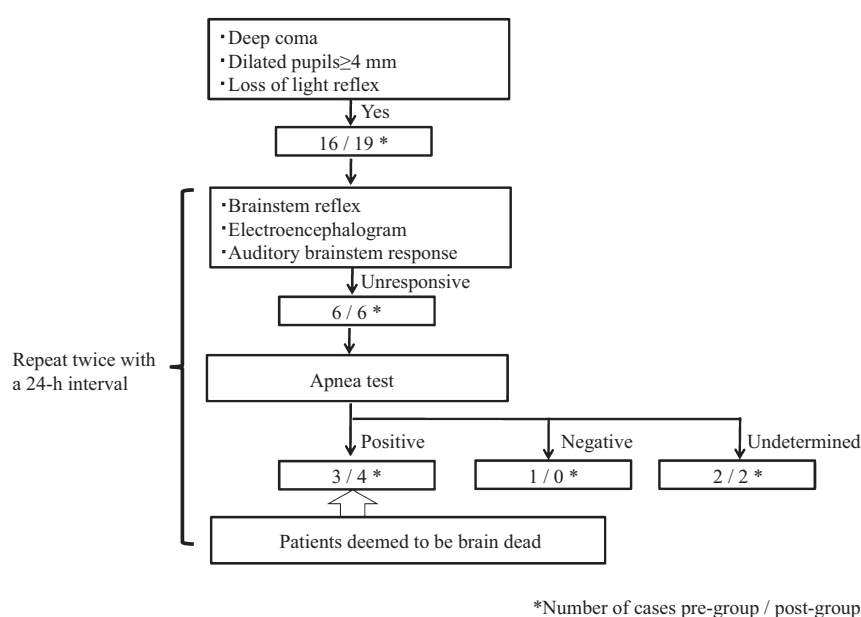
In all cases undergoing a basic determination of brain death (Fig. 2), we obtained family consent before the determination was done.

During the first period, in 6 of the 16 patients who underwent a basic determination of brain death, there were absences of brainstem reflexes, brain waves, and auditory brainstem response. Two of these patients were excluded from the adaptation of the apnea test because their general condition was unstable. The remaining 4 patients had the apnea test; the results were positive in 3 patients and negative in 1. After an interval of at least 24 h, a basic determination

of brain death was repeated in the 3 patients with a positive apnea test and the same result was obtained. In 16 patients who underwent a basic determination of brain death, they met the following exclusion criteria for legal determination of brain death: child abuse or suspected abuse ( $n = 6$ ), mental retardation ( $n = 3$ ), metabolic or endocrine disorder ( $n = 2$ ), and age less than 12 weeks old ( $n = 1$ ) (some fitted into more than one category; see Table 4).

During the second period, in 6 of the 19 children who underwent a basic determination of brain death, there were absences of brainstem reflexes, brain waves, and auditory brainstem response. Two of these patients were excluded from the adaptation of the apnea test because their general condition was unstable. The remaining 4 patients had the

**Fig. 2.** Outcomes of basic determination of pediatric brain death at the National Medical Center for Children and Mothers, Tokyo, Japan. Post-group, cases admitted to the Pediatric Intensive Care Unit July 2010–June 2012, following revision of Japan's Organ Transplantation Act; pre-group, cases admitted to the Pediatric Intensive Care Unit July 2008–June 2010.



**Table 4.** Exclusion criteria for legal determination of brain death in children aged ≤15 years in Japan

Child abuse or suspected abuse	Mental retardation	Metabolic or endocrine disorder	Age <12 weeks	Pre-indicated group	Post-indicated group
				$n = 16$	$n = 19$
+	–	–	–	3	3
+	–	+	–	2	0
+	–	–	+	1	0
–	+	–	–	3	7
–	+	+	–	0	1
–	–	–	+	0	2
–	–	–	–	7	6

Cases were divided according to whether basic determination of brain death was carried out (indicated-group) or not (non-indicated-group).

apnea test that was positive in 4 patients. After an interval of at least 24 h, a basic determination of brain death was repeated in the 4 patients with a positive apnea test and the same result was obtained. In 13 of the 19 patients who underwent a basic determination of brain death, they met the following exclusion criteria for legal determination of brain death: child abuse or suspected abuse ( $n = 3$ ), mental retardation ( $n = 8$ ), metabolic or endocrine disorder ( $n = 1$ ), and age less than 12 weeks old ( $n = 2$ ) (some fit into more than one category; see Table 4).

Only 3 of the patients who had a positive apnea test result did not meet any of the exclusion criteria for legal determination of brain death, which consisted of 0.1% of total PICU admissions and 7% of total PICU deaths. The guardians of these 3 patients were notified of the results of the basic determination of brain death, and they were informed that it was possible to receive a legal determination of brain death only if they agreed to the organ donation after brain death. The consent for organ donation was not obtained from any of these guardians, thus legal determination of brain death was not performed in these 3 patients.

There were differences in the portion of victims resuscitated and the admission route among patients admitted to PICU. However, there were no changes in characteristics of the patients who underwent the basic determination of brain death. Many of the patients undergoing a determination of brain death were admitted after resuscitation (pre-group / post-group, 50%/74%) and many of them were transferred from the emergency department (94%/ 89%). After revision of the Act, only 3 children were deemed to be brain deaths in our hospital, which consisted of 0.1% of total PICU admissions ( $n = 2,009$ ) and 7% of total PICU deaths ( $n = 43$ ).

## DISCUSSION

IN 2011, A total of 5,099 children aged younger than 15 years died in Japan, but they only accounted for 0.4% of all deaths. During the survey period of 2 years, 87% of Japanese hospitals reported five or fewer child deaths among their pediatric patients and only 4% reported 10 or more child deaths. Thus, the general situation is that very few children die at a single institution.

Our hospital treats the greatest number of critically ill children in a single center in Japan, with over 30,000 emergency room visits and over 1,000 PICU admissions each year. So, a relatively large number of children (approximately 20 per year) die at our institution. Moreover, even before revision of the Organ Transplantation Act, we used a basic determination of brain death to predict the neurological prognosis of patients and we devised a system for streamlining the process of making a determination of pediatric brain

death. On the basis of the above considerations, although this study was carried out at a single center, it was considered to be an appropriate environment for investigating the circumstances surrounding pediatric brain death in Japan.

In 2012, 2 years had elapsed since the Organ Transplantation Act was revised on July 17, 2010, but only two children had become brain dead donors.<sup>1</sup> Even though a relatively large number of children die compared with the national average, only three children were deemed to be brain dead and no legal determination of brain death was carried out at our hospital after revision of the Act. In contrast, 8,125 organ transplantation procedures from cadaver donors were performed in 2011 in the USA, with 881 being from children younger than 17 years, most of whom were brain deaths.<sup>2</sup> The reasons why pediatric brain death is much less frequent in Japan than in other countries are discussed below.

It has been reported that brain death among the patients admitted to PICU accounted for 37% of total PICU deaths (93/248) in the USA<sup>3</sup> and 15% (135/907) in Canada.<sup>4</sup> In this study, we found that only three patients were deemed to be brain dead, which accounted for 7% of total PICU deaths. The incidence was much less frequent than in other countries.

## Procedure for legal determination of brain death

At the time these studies<sup>3,4</sup> were reported, repeated determinations of brain death were not required in the USA or Canada. Investigation of the procedures of determining brain death revealed that only 12% (11/93) of the children diagnosed as brain dead in the USA and 7% (63/135) of those diagnosed in Canada underwent the apnea test at least twice. This suggests that some children who were diagnosed as brain dead outside Japan may not have been declared if the Japanese criteria for legal determination of brain death, including the repetition of apnea testing, were applied. There have also been reports regarding failure to follow correct protocols for the determination of brain death, suggesting that some children who were diagnosed as brain dead may not have been declared if the specified criteria were strictly followed.<sup>3,4</sup> For legal determination of brain death, the irreversibility of the patient's state must be properly evaluated. Therefore, it is considered essential to undertake an assessment of brain death at least twice by a procedure that includes the apnea test.

## Exclusion criteria for legal determination of brain death

Exclusion criteria for legal determination of brain death is defined as follows: the patient's unstable general condition,



newborn infants of less than 37 weeks' gestation in the USA,<sup>5</sup> and those of less than 36 weeks' gestation in Canada.<sup>6</sup> In contrast, in Japan, determination of brain death cannot be carried out in pediatric patients with mental retardation and those with metabolic or endocrine disorders, infants of less than 12 weeks' gestation, or in cases where child abuse is confirmed or suspected.

In this study, 22 patients met the exclusion criteria for legal determination of brain death. These patients accounted for 63% of the 35 patients who underwent a basic determination of brain death (Table 4). These results suggest that differences in the exclusion criteria for determination of brain death may influence the number of pediatric brain deaths.

In Japan, brain death is diagnosed in very few adult patients as well as pediatric patients. Organ transplantation from brain dead donors aged 15 years or older has been carried out since its legalization in 1997. After revision of the Organ Transplantation Act, the number of organ transplantations from brain dead donors aged 15 years or older has increased. However, they accounted for only 0.003% of the 1,240,000 persons who died that year. In the USA, organs were transplanted from 7,244 cadaver donors aged 18 years or older in 2011, most of whom were brain dead,<sup>2</sup> and they accounted for 0.3% of the 2,470,000 persons who died that year. Thus, among persons aged 15 years or older, who account for the vast majority of the population and in whom determination of brain death has been carried out for more than 10 years in Japan, the rate of organ transplantation from brain dead donors is still less than 1/100th of that in the USA. Therefore, as pediatric brain deaths only account for 0.4% of total deaths and the number of children dying is accordingly quite low, it seems reasonable for there to be few Japanese children in whom brain death is declared.

Another factor is that the Organ Transplantation Act defines brain death as human death only when a transplant is to be carried out, and brain death is still not widely accepted as human death. In this study, the guardians of all the patients who were deemed to be brain dead following a basic determination of brain death were notified of the results and were informed that organ donation was possible. However, none of the guardians gave consent for organ donation and thus a legal determination of brain death was not performed in any of these patients. Brain death has always been an issue that deserves to be discussed separately from transplantation. In the future, it is important to spread the concept of brain death correctly in Japan. Furthermore, determination of brain death needs to be discussed as an option for patients receiving terminal care in end-of-life.

As Mejia *et al.*<sup>3</sup> have reported, we also found that many children undergoing a basic determination of brain death had been resuscitated after cardiac arrest or transferred from the

emergency department. Therefore, although brain death is rare in pediatric patients, it can be expected to be more common at hospitals that provide emergency care. So, it is necessary to develop a system for dealing with pediatric brain death at all hospitals that may provide emergency care to children. In preparation, it is therefore essential to create a protocol for the determination of pediatric brain death that also covers abused children, and to perform simulation training using this protocol.

This study was carried out at a single pediatric facility and may have some kind of bias in the study sample. Accordingly, a nationwide study to evaluate the incidence and characteristics of pediatric brain death should be conducted in the future.

## CONCLUSIONS

THIS STUDY EVALUATED the incidence and characteristics of pediatric brain death in a pediatric hospital. The low incidence of pediatric brain death in Japan may be due to differences of exclusion criteria for determination of pediatric brain death and personal views regarding life and death compared with other countries.

This article is based on a study first reported in *J. Jpn Assoc. Acute Med.* 2013; 24: 925–32.

## CONFLICT OF INTEREST

NONE.

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